POLICY STATEMENT REGARDING PREGNANCY TESTING

6/5/2014

The Duke University Health System (DUHS) Institutional Review Board (IRB) has determined that all females who are of child-bearing potential being considered for participation in a research study, in which there is a possibility of harm to a fetus from the study interventions, must have a negative pregnancy test before undergoing any study-related activities with a potential risk to a fetus.

Protocols where the study interventions themselves do not pose a potential risk to a fetus, even if the interventions the individual may undergo for routine or standard care are greater than minimal risk, (for example, a study where the intervention was the collection of blood samples following surgery that is part of the individual's routine care) would not require pregnancy testing or the use of contraception.

HARM VERSUS BENEFIT – FDA Pregnancy Categories

Current FDA pregnancy categories reflect the balance of potential benefits and harms, rather than an increasing scale of risk:

Pregnancy Category A - Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Pregnancy Category B - Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Pregnancy Category C - Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Pregnancy Category D - There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Pregnancy Category X - Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Although in most cases exclusion of pregnant women from research studies is justifiable based on uncertainty about fetal risks or on the potential effect of the physiological changes accompanying pregnancy on measures and outcomes of interest, there may be circumstances where the potential benefits to mother and/or fetus outweigh the risks—for example, in the case of a potentially life-threatening condition in the mother that poses a greater risk to a fetus than study interventions. Such cases must be considered by a convened IRB with appropriate expertise present prior to the onset of any study activities.

DEFINITION OF "CHILD-BEARING POTENTIAL"

Female subjects are considered "of child-bearing potential" if they (a) are anatomically and physiologically capable of becoming pregnant and (b) they will be, or could possibly be, engaging in sexual activity with males while study interventions that pose the possibility of harm to a fetus are occurring. Note that this time period also includes any time after study activities have ended where the protocol specifies the use of contraception.

Females with documented congenital or acquired disorders that are incompatible with pregnancy are not considered "of child-bearing potential." A history of a diagnosis of, or treatment for, infertility is not in itself sufficient to exclude a subject from the need for pregnancy testing and contraception.

Women who have had a hysterectomy or a bilateral oophorectomy are not considered "of child-bearing potential". If a study population by definition would be restricted to women with a previous history of one or both of these procedures (e.g., certain pelvic cancer protocols), and the protocol calls for inclusion of pregnancy testing and contraceptive language, a rationale for the inclusion of this language should be provided.

Sterilization (tubal ligation/cauterization or vasectomy of the male partner), while highly effective, does not perfectly prevent pregnancy. Women using these contraceptive methods are considered "of child-bearing potential."

For girls of normal reproductive potential, the possibility of becoming pregnant requires ovulatory menstrual cycles and heterosexual intercourse. Although the timing of ovulation relative to menarche is variable, there is consistent evidence that some girls may have ovulatory cycles prior to menarche, and that, in healthy populations, regular ovulation may begin within a few months of menarche. Therefore, menarche is the most feasible clinical indicator of the biological potential for pregnancy.

The median age of menarche in the US is 12.4 years, with less than 10% of girls experiencing menarche before age 11 but over 90% by age 14[1]. Age at first intercourse for females varies; 3% or less of females will have had first intercourse before age 12, but at least 20% of females in most ethnic groups will have had intercourse by age 15[2].

- Girls under the age of 12 who have not had their first period can be considered "not of child-bearing potential."
- Girls between the ages of 12 and 14 who have not yet had their first period can be considered "not of child-bearing potential" if study activities posing a possible risk to a fetus will last less than 1 month and menarche does not occur between the initial study visit and the start of relevant study activities.
- Girls 12 and older who are potential subjects in protocols where study activities posing possible risks to a fetus will last longer than 1 month, or girls who have had their first period, should be considered " of child-bearing potential."

The median age of menopause in the US, defined as 12 months of amenorrhea, is 51 years; by age 48, approximately 15% of women will be postmenopausal, while virtually 100% will be post-menopausal by age 55[3]. Women are considered past the age of "child-bearing potential" if

- they are greater than 55 years of age, OR
- they are at least 50 years of age AND
    - have not menstruated for at least **12** months, OR
    - have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL.
- they are at least 45 years of age AND
    - have not menstruated for at least **18** months, OR
    - have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL.
- For drugs classified, or likely to be classified, as FDA Category X, the duration of amenorrhea for women of all ages must be 24 months, consistent with FDA labeling of these drugs.

RATIONALE FOR PREGNANCY TESTING

Once the investigator has determined that the study intervention(s) pose a potential risk to a fetus or that inclusion of pregnant women would affect the integrity of the study data, then a method for ruling out pregnancy prior to the onset of study interventions must be part of the study design.

The key attribute of this method must be a high negative predictive value (i.e., a very high probability that a woman of childbearing potential with a negative test is truly not pregnant and will not become pregnant prior to beginning study procedures).[1]

The following information should be considered when developing the pregnancy testing and contraceptive requirements for a given research study:

1. **Factors which affect the sensitivity of the pregnancy test**.

[1] The negative predictive value is directly related to (a) the sensitivity of the pregnancy test being used (negative predictive value will be higher as the sensitivity of the test *increases*), and (b) the probability that a woman is pregnant at the time of the test (the negative predictive value will be higher as the probability that a woman is pregnant *decreases*.)

- Serum vs. urine testing—serum tests generally are able to detect human chorionic gonadotropin ("hCG") at a level of 5 mIU/mL, while laboratory-based urine tests have a lower limit of detection of 20-25 mIU/mL.
- Specific testing kit—sensitivities for urine assay kits vary; in addition, particularly for home kits, there is substantial user variability in the accuracy of results[4]
- Timing of the test during the menstrual cycle—hCG is produced only after implantation, which occurs approximately 7 days after ovulation. In a normally developing pregnancy, hCG levels double every 2 days. Both serum and urine tests will be negative if the pregnancy test is administered before ovulation, and both will be positive after the expected first day of the next menstrual period. There is a 3-5 day window during very early pregnancy (before the first day of the expected next menstrual period) where a serum test will be positive while a urine test will be negative.

2. **Factors which affect the likelihood that a woman will be pregnant at the time of testing**.

- Age—fertility is strongly and inversely related to age. Adolescents and women in their early 20s have the highest fertility rates, while fertility rates decline sharply after age 35.
- Contraceptive method—The effectiveness of contraceptive methods in "typical use" ranges from greater than 99% for sterilization, IUDs, and implantable hormonal contraception to 90-95% for oral, injectable, and topical hormonal contraceptives to 75-90% for barrier methods with spermicide.[5].
- Duration of method use—failure rates for all methods are highest in the first 3-6 months after beginning use.
- Pre-existing illness—many chronic conditions can adversely affect fertility

The likelihood of pregnancy among women "of child-bearing potential" is highest in healthy women in their late teens and early twenties who have just begun using a barrier or non-injectable hormonal method, while it is lowest in women in their forties with chronic illness who have been using sterilization or an IUD for over 6 months—therefore, the risk of a false negative test will be higher in younger women even if the same pregnancy test is used.

Questions about developing an appropriate pregnancy testing and contraceptive regimen for a given study can be directed to a Chair in the IRB or to Dr. Evan Myers or his designee in Obstetrics and Gynecology. You can also contact the DUHS Drug Information Center at 919.684.5125 for additional FDA pregnancy risk class information and to research literature on the potential risks to the mother or fetus.

A pregnancy testing plan that does not fall within the specifications of this policy must be reviewed by a convened IRB. IRB approval is required prior to implementation of a pregnancy testing plan, whether submitted at the time of initial protocol review or under an amendment. The research summary and/or protocol should provide the details of and rationale for the pregnancy testing plan and the consent form should inform subjects of the testing requirements, timing of the test, any risks involved, and what contraceptive practices, if any, are required for study participation.

SERUM PREGNANCY TESTING:
If a serum pregnancy test will be used to exclude pregnant women from the study, the test must measure the concentration of hCG human serum that was collected no more than 48 hours before initiation of study activities with a potential risk to a fetus**,** such as the administration of a study drug or placement of a study device. The pregnancy test must be conducted and analyzed by a CLIA-accredited laboratory, but the laboratory is not required to be affiliated with DUHS.

If the protocol requires a serum pregnancy test at the initial screening visit in order to document eligibility, but the first study activity with a potential risk to a fetus will not occur for 48 hours or more, the subject must be required to practice appropriate contraception during this period of time and this should be specified in the study protocol and consent form. Otherwise, a repeat serum pregnancy test is required.

If a subject begins the use of contraception at the time of study enrollment to meet these requirements, and either the risk of pregnancy is high (healthy women in their late teens and early twenties who have just begun using a barrier or non-injectable hormonal method) or the potential risks to a fetus from the study interventions is high (such as administration of FDA pregnancy class D or X drugs, use of radiation, major surgery), it is recommended that the pregnancy test be repeated prior to the administration of study intervention(s) that may pose a risk to a fetus. In this case, a urine pregnancy test may be used (as described below). Subjects who have been using a consistent contraceptive method for at least 3 months prior to enrolling in the study (as part of their normal routine, not as mandated by the study) would not necessarily need a second pregnancy test.

The pregnancy testing plan must be approved by the IRB at the time of initial protocol review, or while reviewing an amendment specifically requesting such a plan. A negative test result **MUST** be obtained prior to the occurrence of any study activities with a potential risk to a fetus.

URINE PREGNANCY TESTING:
A urine pregnancy test may be used to exclude pregnant women from the study if all of the following conditions are met and specified in the protocol:

1) Any study drugs being administered to subjects are U.S. Food and Drug Administration (FDA) pregnancy class A, B, or C.

2) The sponsor of the study does not require a serum pregnancy test to exclude pregnant women.

3) The subject has been using a medically acceptable contraceptive for at least 3 months prior to study enrollment **OR** the subject a) has a regular menstrual cycle, b) Day 1 (onset of menses) for the current cycle is known, and c) the urine pregnancy test can be administered within the first two weeks of the current cycle (between Days 1 and 14).

Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Note that, depending on the study population or design, some contraceptive methods may not be appropriate (for example, oral contraceptives are generally contraindicated in the perioperative period because of the increased risk of venous thromobosis associated with their use, or study drugs may affect the metabolism of oral contraceptives, reducing their effectiveness). The standard contraceptive language should be modified to reflect medically acceptable contraceptives for the study population and the study interventions to be conducted, based on standard guidelines[6], or in consultation with an obstetrician-gynecologist.

4) The urine pregnancy test is administered and interpreted by the DUHS clinical laboratories or by an individual who has completed competency training from the Duke Office of Clinical Research (DOCR).

5) The urine pregnancy test used must be the commercially available test kit(s) specified by DOCR (please check website at docr.som.duke.edu for list of currently approved test kits).

6) Home pregnancy kits, including those provided by sponsors, are not acceptable for the purposes of excluding pregnant women from research protocols. This is because of (a) the high degree of variability in the accuracy and interpretation of home pregnancy kits, (b) the technical issues involved with verifying a negative result from a home test, and (c) the ethical issues involved in requiring a subject to self-report an unverifiable result which might end up excluding her from participation in research or lead to unnecessary risk to her or a fetus.

If the FDA pregnancy class for one or more of the study drugs is unknown, all of the following conditions must also be met:

A) None of the study drug(s) in question belong to any of the following classes of drugs: angiogenesis inhibitors, retinoic acid derivatives, endocrine disruptors, chemotherapeutic drugs, thalidomide derivatives or thalidomide-like drugs, or any other class of drugs with known potential risks to a fetus.

B) A convened IRB has approved the use of the urine pregnancy test for the study in question.

C) Conditions 2-5 above are met.

The flow chart appended to this policy may be used to help determine if use of a urine pregnancy test is appropriate, but use of a urine pregnancy test to exclude pregnant women must be approved by the IRB at the time of initial protocol review, or while reviewing an amendment specifically requesting such a plan.

If a urine pregnancy test will be used to exclude pregnant women from the study, administration of the test should occur within one hour after collection of the urine. If this is not possible, the sample must be refrigerated and tested within 48 hours of collection and no more than 48 hours prior to the initiation of study activities with a potential risk to a fetus**,** such as the administration of a study drug or placement of a study device. A negative test result **MUST** be obtained prior to the occurrence of any study activities with a potential risk to a fetus.

If a subject begins the use of contraception at the time of study enrollment to meet these requirements, and either the risk of pregnancy is high (healthy women in their late teens and early twenties who have just begun using a barrier or non-injectable hormonal method) or the potential risks to a fetus from the study interventions is high (such as administration of FDA pregnancy class D or X drugs, use of radiation, major surgery), it is recommended that the pregnancy test be repeated prior to the administration of study intervention(s) that may pose a risk to a fetus. In this case, a urine pregnancy test may be used (as described below). Subjects who have been on contraception for at least 3 months prior to enrolling in the study (as part of their normal routine, not as mandated by the study) would not necessarily need a second pregnancy test. The pregnancy testing plan must be approved by the IRB at the time of initial protocol review, or while reviewing an amendment specifically requesting such a plan.

Once a negative pregnancy test result is obtained, whether using a serum or urine pregnancy test, appropriate contraceptive measures must be maintained by all sexually active women of child-bearing potential during the study until all potential risks to the fetus have ended, and this must be specified in the study protocol and consent form. Please see standard contraceptive language on the IRB web site.

Pregnancy Testing for Research using MRI without Contrast Enhancement

The IRB will permit urine pregnancy testing for women of childbearing potential who agree to participate in research using Magnetic Resonance Imaging (MRI) without contrast enhancement, using equipment with magnets that are 4 Tesla in strength or less, provided all of the following criteria are met:

1) The research must **not** involve any study procedures or interventions where a possibility of harm to a fetus may occur, other than through the use of the MRI.
2) All subjects who are women of child-bearing potential must receive a urine pregnancy test on the day the subject will receive a research MRI without contrast enhancement.
3) The urine pregnancy test result must be negative before the MRI examination may proceed.

4) If the subject will be asked to have an MRI without contrast enhancement on more than one day, the study protocol and consent form must stipulate either the use of effective contraceptive measures during that portion of the study, or additional pregnancy testing must occur each day the subject will be asked to undergo such an MRI.
5) The individual administering a urine pregnancy test must have completed competency training from the Duke Office of Clinical Research (DOCR). The urine pregnancy test used must be the commercially available test kit(s) specified by DOCR (please check website at docr.som.duke.edu for list of currently approved test kits).

Training:

The individual performing a urine pregnancy test must have documentation of competency training from the Duke Office of Clinical Research (DOCR).

The urine pregnancy test used must be the commercially available test kit(s) specified by DOCR (please check website at docr.som.duke.edu for list of currently approved test kits). Documentation of the administration of the urine pregnancy test and its result will be included in the subject's research record in a form and format specified by DOCR.

Training information can be obtained from DOCR at docr.help@dm.duke.edu or (919) 681-6665.

Follow-up Pregnancy Testing throughout a Research Protocol:

This section applies to any research protocol that involves a product, treatment, or procedure for which follow-up pregnancy testing would be standard of care (e.g., thalidomide, isotretinoin, ribavirin, etc.), or for a new (investigational) drug expected to have similar risks as drugs such as thalidomide, isotretinoin or ribavirin. For such protocols, follow-up urine or serum pregnancy testing must use kits that meet Duke standards, as described in the policy above.

The most rigorous pregnancy testing schema that applies to the study is the one that must be followed. For example, studies that involve lenalidomide will follow the requirements under RevAssist from the FDA and the HRPP policy on lenamlidomide/thalidomide. These requirements would override less rigorous pregnancy testing plans otherwise permitted under this policy.

For any other protocol where the follow-up pregnancy testing is for research purposes only and not to protect a fetus (e.g., pregnancy testing that would only be done because the subject is enrolled in the study), the sponsor's kit would be acceptable because (1) there is no current industry or FDA standard for selecting pregnancy tests solely for research purposes, and (2) there is substantial variability between kits, which could create issues for sponsors in terms of data integrity as well as basic feasibility if each site used a different kit. This acceptance would be conditional on the sponsor providing

assurances that either the sponsor or the Clinical Research Organization (CRO) will provide training and ongoing Quality Control (QC) on the use of the kit.

No home pregnancy testing is acceptable, whether the testing kits are provided by the sponsor or obtained from other sources, for the reasons cited in the policy above.

This section does not apply to protocols where pregnancy tests are repeated throughout the study because subjects are not required to use contraception but are undergoing repeated procedures that pose a potential risk to a fetus (such as MRIs with contrast or ionizing radiation). For such protocols, the pregnancy testing kits used must meet Duke standards, as described in the policy above.

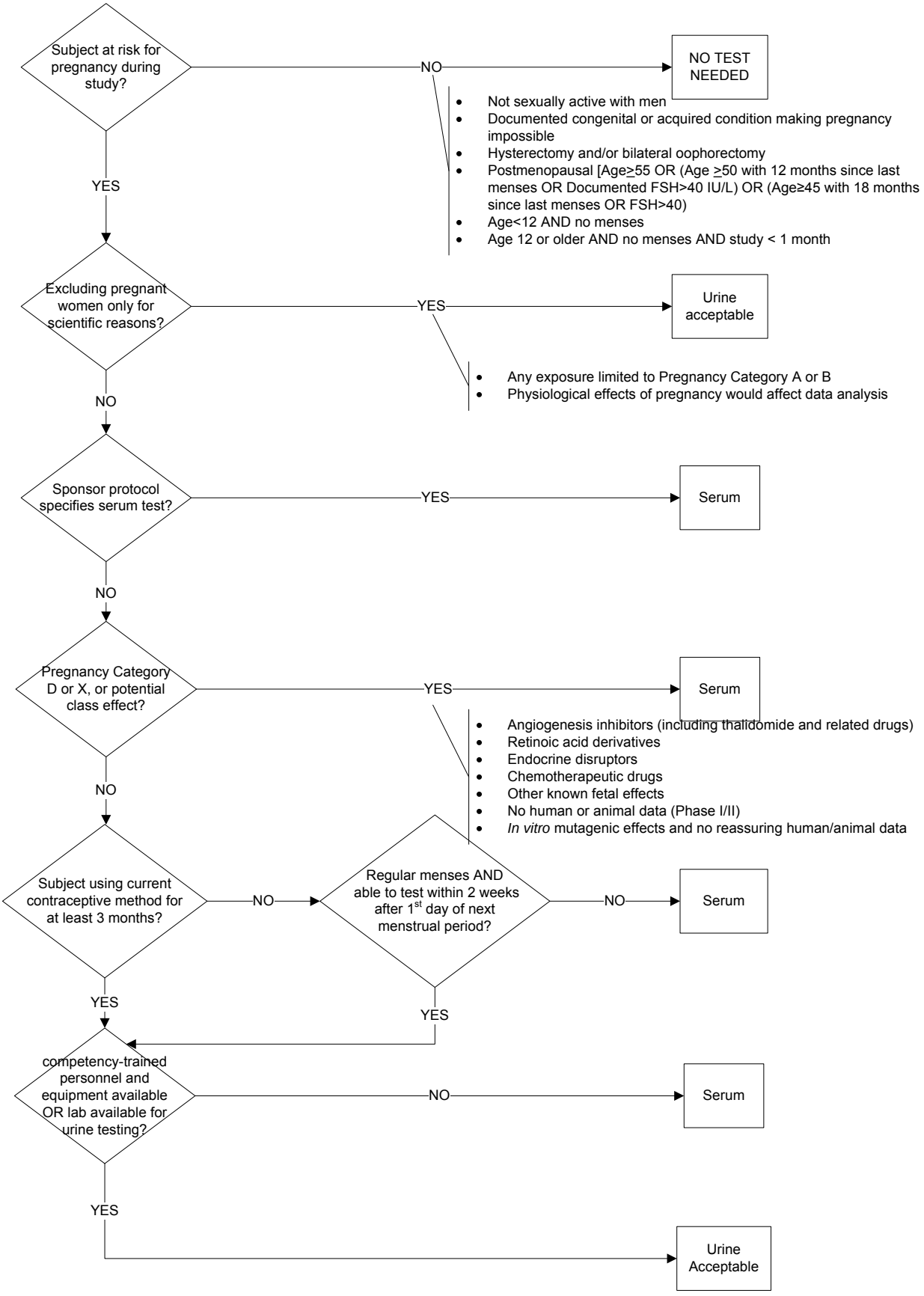
Please note that Appendices A, B, and C follow:
APPENDIX A: FLOW CHART FOR PREGNANCY TESTING – SERUM VS. URINE
APPENDIX B: Numbing and Dilating Eye Drops Used in Research
APPENDIX C: Examples of Pregnancy Class D and Class X Drugs

References:

1. Chumlea WC, Schubert CM, Roche AF, et al. Age at Menarche and Racial Comparisons in US Girls. Pediatrics 2003;111:110-3.
2. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, et al. Age of sexual debut among US adolescents. Contraception 2009;80:158-62.
3. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153:865-74.
4. Cole LA, Khanlian SA, Sutton JM, Davies S, Rayburn WF. Accuracy of home pregnancy tests at the time of missed menses. Am J Obstet Gynecol 2004;190:100-5.
5. http://www.contraceptivetechnology.org/table.html
6. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_w

NEXT PAGE:

APPENDIX A: FLOW CHART FOR PREGNANCY TESTING – SERUM VS. URINE


Subject at risk for pregnancy during study?
NO
NO TEST NEEDED
Not sexually active with men
Documented congenital or acquired condition making pregnancy impossible
Hysterectomy and/or bilateral oophorectomy
Postmenopausal [Age≥55 OR (Age ≥50 with 12 months since last menses OR Documented FSH>40 IU/L) OR (Age≥45 with 18 months since last menses OR FSH>40)
Age<12 AND no menses
Age 12 or older AND no menses AND study < 1 month
YES
Excluding pregnant women only for scientific reasons?
YES
Urine acceptable
Any exposure limited to Pregnancy Category A or B
Physiological effects of pregnancy would affect data analysis
NO
Sponsor protocol specifies serum test?
YES
Serum
NO
Pregnancy Category D or X, or potential class effect?
YES
Serum
Angiogenesis inhibitors (including thalidomide and related drugs)
Retinoic acid derivatives
Endocrine disruptors
Chemotherapeutic drugs
Other known fetal effects
No human or animal data (Phase I/II)
In vitro mutagenic effects and no reassuring human/animal data
NO
Subject using current contraceptive method for at least 3 months?
NO
Regular menses AND able to test within 2 weeks after 1st day of next menstrual period?
NO
Serum
YES
YES
competency-trained personnel and equipment available OR lab available for urine testing?
NO
Serum
YES
Urine Acceptable

APPENDIX B – Numbing and Dilating Eye Drops Used in Research

Applicability – to exclude pregnant women from a research study when the only potential risks to a fetus are from the administration of one or more of the dilating and/or numbing drops listed in the table below in research studies.

For the drugs/dosages listed below, used in accordance with their FDA approved labeling, the following procedures may be used to exclude pregnant women for scientific purposes and/or because of the potential risks to a fetus.

1. ***Normal volunteers for single study visit:***
Female subjects who are of child-bearing potential (as defined in the main policy) will be questioned about the date of last menstrual period and whether they are pregnant, trying to get pregnant, using contraceptives, and/or sexually active. If documented that it is *unlikely* the potential subject is pregnant or could be pregnant, then she can continue study participation and receive dilating and/or numbing eye drops with the use of punctual occlusion techniques to minimize systemic delivery. If there is a concern that the subject could be pregnant for any reason, a urine pregnancy test will be administered in accordance with HRPP policy and the test must be negative for the subject to continue study participation. If the subject or investigator chose not to initiate the pregnancy test as detailed, then the subject must be withdrawn from the study. Women who are nursing will also be excluded unless the protocol has prior IRB approval to enroll them.

2. ***Normal volunteers or patients with specific eye conditions already entered as study subjects in an IRB approved study and who are returning for serial study visits requiring eye numbing/dilation for study purposes, and who are of child-bearing potential:***
At each visit, female subjects who are of child-bearing potential will be questioned about the date of last menstrual period and whether they are pregnant, trying to get pregnant, using contraceptives, and/or sexually active. If documented that it is *unlikely* the potential subject is pregnant or could be pregnant, then she can continue study participation and receive dilating and/or numbing eye drops with the use of punctual occlusion techniques to minimize systemic delivery. If there is a concern that the subject could be pregnant for any reason, a urine pregnancy test will be administered in accordance with HRPP policy and the test must be negative for the subject to continue study participation. If the subject or investigator chose not to initiate the pregnancy test as detailed, then the subject must be withdrawn from the study.

An alternative would be that at the first study visit, a urine pregnancy test is administered and if it Is negative, the subject can continue study participation and will be required to either use contraception for the duration of the study (and to inform study doctor if she thinks she may be pregnant) or have the urine pregnancy test administered at every study visit.

Women who are nursing will also be excluded unless the protocol has prior IRB approval to enroll them.

3. ***Subject recruited from clinic but whose eyes are already dilated/numbed as part of SOC eye visit for inclusion into study on the same day:***
NO additional history or testing would be required, unless other study interventions pose a potential risk to the fetus.

Definition - A woman of child-bearing potential is “unlikely to be pregnant” in accordance with HRPP policy if:

1. She is not sexually active with males;
2. She is sexually active with males but has regular menses, based on the date of her last menstruation she has not missed a period, and the date of the study visit is at least 7 days before her period would be due (when both serum and urine pregnancy tests would be negative); or
3. She is sexually active with males but has been on medically acceptable hormonal contraceptives (as defined in the current HRPP policy) for at least 3 months or had an intrauterine device (IUD) placed at least 3 months ago, and she does not report any concerns or problems with her contraceptive method or that she may be pregnant when asked.

Women with tubal ligations or with male partners who have had a vasectomy must still meet one of the above criteria to be considered “unlikely to be pregnant.”

Dilating and Numbing Eye Drops and Dosages

Name of Drug	Available Concentrations	Strengths used at Duke Eye Center	FDA Pregnancy Rating	Comments
Proparacaine HCl ophthalmic solution	0.5%	-Used alone as the **0.5% solution**	C	These drugs are all being used for indicated purposes at approved doses and concentrations.
Phenylephrine ophthalmic Solution	0.12%, 2.5%, 10%	-Used alone as the **2.5% concentration** **-**Also used in the **Duke Eye Mix (tropicamide 0.5% and phenylephrine 5%)** **-**Also used as the **Peds Mix (cyclopentolate 1% and phenylephrine 2.5%)**	C	
Tropicamide ophthalmic Solution	0.5%, 1%	-Used alone as the **1% solution** -Also used in the **Duke Eye Mix (tropicamide 0.5% and phenylephrine 5%)**	C	
Cyclopentolate ophthalmic Solution	0.5%, 1%, 2%	-Used alone as the **1% solution** -Also used in the **Peds Mix (cyclopentolate 1% and phenylephrine 2.5%)**	C	

APPENDIX C
Examples of Pregnancy Class D and Class X Drugs

(adapted from Briggs' Drugs in Pregnancy and Lactation, Appendix pages 2029-2045)
This is not a comprehensive list. Please refer to a reputable drug reference for ratings of newly FDA-approved drugs and ratings of Drugs in Pregnancy classes A, B, and C

Miscellaneous Anti-Infectives	Antineoplastics (continued)
carbarsone	doxorubicin
Amikacin	epirubicin
voriconazole	idarubicin
	aminopterin
Anti-Malarials	clofarabine
Quinine	cytarabine
	fluorouracil
Antivirals	mercaptopurine
Ribavirin	methotrexate
	thioguanine
Iodine	paclitaxel
Iodine	vinblastine
povidone-iodine	vincristine
	vinorelbine
Tetracycline	azacitidine
doxycycline	decitabine
tigecycline	nelarabine
	irinotecan
Antilipemic agents	topotecan
atorvastatin	etoposide
cerivastatin	teniposide
fluvastatin	erlotinib
Lovastatin	gefitinib
pravastatin	vorinostat
rosuvastatin	leuprolide
simvastatin	tamoxifen
	temozolomide
Antineoplastics	procarbazine
Busulfan	gemtuzumab
chlorambucil	ibritumomab
cyclophosphamide	sorafenib
ifosfamide	carboplatin
mechlorethamine	cisplatin
Mephalan	bortezomib
carmustine	dasatinib
streptozocin	imatinib
mitoxantrone	sunitinib
bleomycin	bexarotene
daunorubicin	tretinoin

Antineoplastics (continued)	Anticonvulsants (continued)
hydroxyurea	mephobarbital
plicamycin	paramethiadone
Thiotepa	phenobarbital
trimetrexate	phensuximide
	phenytoin
Sympatholytics	primidone
dihydroergotamine	trimethiadone
ergotamine	valproic acid
	SSRIs
Bisphosphonates	paroxetine
pamidronate	
zoledronic acid	**Anti-Migraine agents**
	dihydroergotamine
	ergotamine
ACE Inhibitors and Angiotensin II antagonists (most ranked C in 1st trimester, D in 2nd & 3rd trimesters)	**Sedatives and Hypnotics**
benazepril	alprazolam
Captopril	bromides
Enalapril	chlordiazepoxide
Fosinopril	chlorazepate
Lisinopril	diazepam
Quinapril	flunitrazepam
Ramipril	flurazepam
trandolapril	lorazepam
	mephobarbital
candesartan	midazolam
eprosartan	oxazepam
Irbesartan	pentobarbital
Losartan	phenobarbital
olmesartan	quazepam
Valsartan	secobarbital
	temazepam
Other antihypertensives	triazolam
Atenolol	
amiodarone	**Smoking Deterrents**
	nicotine replacement therapy
Vasodilators	
Bosentan	**Tranquilizers/Antipsychotics**
	lithium
Anticonvulsants	
carbamazepine	
clonazepam	

Dermatologic Agents	Pituitary
Etretinate	leuprolide
isotretinoin	
tazarotene	**Progestogens**
	ethisterone
Diagnostic Agents	ethynodiol
Iodine derivatives	medroxyprogesterone
	norethindrone
Antisecretory Agents	norethynodrel
misoprostol	norgestrel
	oral contraceptives
Gallstone Solubilizing Agents	
Chenodiol	**Immunologic Agents**
	lenalidomide
Anticoagulants	thalidomide
warfarin (and other coumarin derivatives)	
	Immunosuppressants
Androgens	azathioprine
Danazol	mycophenolate mofetil
fluoxymesterone	everolimus
methyltestosterone	
testosterone	**Antirheumatic agents**
	leflunomide
Antiestrogens	methotrexate
Tamoxifen	
	Oxytocics
Antiprogestogen	misoprostol
mifepristone	
	Psoralens
Antithyroid	acitretin
carbimazole	etrinate
methimazole	
propylthiouracil	**Radiopharmaceuticals**
sodium iodide	Sodium iodide^{125}
	Sodium iodide^{131}
Estrogens	
chlorotriansene	**Vitamin A derivatives**
clomiphene	etretinate
dienestrol	isotretinoin
diethylstilbestrol	tretinoin (systemic)
Estradiol	
estrogens, conjugated	
Estrone	
ethinyl estradiol	
mestranol	
oral contraceptives	

Previous Version Date(s): 06/25/2008, 04/03/2009, 04/30/2009, 10/25/2011, 01/14/2013, 07/22/2013